

Remarks

Claims 2-14 are pending in the present application. Claims 12-15, as filed in the original application, were renumbered by Preliminary Amendment to read as claims 11-14.

Claim 1 has been canceled without prejudice. Claim 2 has been amended by adding the step of contacting the test substance with control cells which do not express COX-2 and determining the level of proliferation of the control cells in the presence of the test substance. Support for this amendment is found throughout the specification as filed, particularly at page 18, line 3 to page 19, line 18, FIG. 3, and FIG. 4. Claims 2, 6, and 11 have been amended to affirmatively recite that the mutant α -subunit induces production of COX-2. Support for this amendment to claims 2, 6, and 11 is found throughout the specification as filed, particularly at page 5, lines 13 and 14, Example 1, FIG. 2A, and FIG. 3.

A. Sequence Compliance

Examiner asserts that Applicants are required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or specification. Applicants note that all sequence identification numbers were properly inserted in the application as filed. Examiner also asserts that a paper copy of the sequences was not provided. A copy of the International Application as published, with sequence listing, was submitted upon entering the national stage under 35 U.S.C. § 371. However, to assist the Examiner, another copy of the paper sequence listing is submitted herewith.

B. Response to 35 U.S.C. § 112, second paragraph, indefiniteness rejection

Claim 1 stands rejected as allegedly indefinite. Claim 1 has been canceled, therefore the rejection as to claim 1 is now moot.

Independent claims 2, 6, 11, and dependent claims 3-5, 7-10 and 12-14, stand rejected as allegedly indefinite. The Examiner states at page 3 that "As applicants appear to determine the inhibition [sic] COX-2 activity, indirectly by measuring parameters which could be due to the test substance itself, it is not clear to the Examiner as to how applicants will differentiate the inherent effect of the test substance itself (if it has any) from the effect due to inhibition of COX-

2.” The Examiner then asserts that without setting up control reactions and comparing the results with test reactions it is not clear as to how it can be concluded that a test substance has the desired property of inhibiting COX-2. The Examiner alleges at page 4 of the Office Action that the claimed methods lack the step of determining that changes in proliferation, prostaglandin levels, or arachidonic acid levels, are the result of COX-2 induction and not another reason. The Examiner further alleges that a step has not been provided to specifically confirm that the method will identify a compound which inhibits a COX-2 that has been specifically induced by the mutant G α 12.

1. Proliferation Level (Claim 2)

Although not necessarily agreeing with the reasoning of the Examiner, claim 2 has been amended by adding a control comprising determining the effect of a test substance on the proliferation of control cells, namely, cells which do not express COX-2. The absence of change in the proliferation of the control cells in response to the test substance indicates that any inhibition of proliferation observed in the indicator cells is due to the test substance’s effect on the COX-2 activity of the indicators cells, and not any other proliferation-affecting cellular mechanism.

The amendment to claim 2 is supported by Example 2 of the specification and is exemplified in FIG. 4. FIG. 4 demonstrates that proliferation of transfected G α 12QL-NIH3T3 cells was greatly inhibited by a COX-2 inhibitor, compared to G α 12QL-NIH3T3 cells not treated with the inhibitor. The COX-2 inhibitor had no effect on cells which do not express COX-2, e.g., control NIH3T3 cells not transfected to express G α 12QL (FIG. 4).

2. Prostaglandin Level (Claim 6) and Arachidonic Acid Level (Claim 11)

The claimed method for screening test substances for COX-2 inhibitory activity by measuring prostaglandin (claim 6) and arachidonic acid (claim 11) levels in indicator cells transfected with the mutant G α 12QL does not require the use of control reactions. One skilled in the art would understand this, based upon the teachings of the specification.

The specification describes engineered indicator cells which express COX-2. The cells are driven to do so by the G α 12QL mutation. Arachidonic acid is the substrate that COX-2 converts to prostaglandin (see DuBois et al., asserted against the claims and discussed below; see particularly FIGS. 1 and 2). Any change in COX-2 activity in the indicator cells will result in arachidonic acid and prostaglandin level changes. A decrease in COX-2 activity will result in accumulation of arachidonic acid and lower prostaglandin levels. Arachidonic acid levels and prostaglandin levels are each direct, not indirect, indicators of COX-2 activity. Because the indicator cells express COX-2, one of ordinary skill in the art would understand that an increase in arachidonic acid or decrease in prostaglandin in the indicator cells would necessarily be attributable to inhibition of COX-2 activity. Examiner has provided no evidence which supports the assertion that modulation of arachidonic acid or prostaglandin level in the indicator cells upon treatment with a test substance could be attributable to a mechanism other than inhibition of the COX-2 enzyme.

One of ordinary skill in the art would understand that a control reaction could be performed, if desired, where arachidonic acid and/or prostaglandin levels are measured in control cells not containing the mutant G α 12QL. However, because it is the activity of COX-2, and no other factor, which determines the levels of arachidonic acid and prostaglandins in the indicator cell, no such control is necessary. Such controls are not essential steps in the claims. A claim need only include essential elements and need not recite detail if a skilled artisan could supply the details from the teachings of the specification. *Cohn v. Comr. Pats.* (DCDC 1966) 251 FSupp 437, 148 USPQ 486; *Ex parte Bull et al.* (POBA 1957) 117 USPQ 302; *Ex parte Biel* (POBA 1962) 137 USPQ 315. Moreover, the absence of a limitation in a claim does not render a claim indefinite if each limitation recited in the claim is definite. *In re Wakefield et al.* (CCPA 1970) 422 F.2d 897, 164 USPQ 636. None of the recited elements of the present claims are indefinite, therefore the absence of an element reciting an additional control reaction does not render the claims indefinite, even if such steps were essential (they are not).

To advance prosecution, independent claims 2, 6, and 11 have been amended to recite the feature that the mutant α -subunit induces production of COX-2. The present application discloses that the mutant G α 12 induces COX-2 expression in cells which do not normally

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express COX-2 (FIGS. 2A, 2B, and 3), and provides such cells as indicator cells (FIGS. 4, 5, 6A, and 6B). Assays are provided for testing indicator cells which have been transfected to express the mutant G α 12 (see Examples and FIGS. 2-6).

Withdrawal of the 35 U.S.C. § 112, second paragraph rejection of these claims is therefore respectfully requested.

C. Response to 35 U.S.C. § 112, first paragraph, enablement rejection

Claims 2-14 stand rejected as allegedly lacking enablement. The Examiner alleges at page 5 of the Office Action that the specification does not reasonably provide enablement for determining that the test substance inhibits activity of a COX-2 which was induced by a mutant GTPase-deficient G α 12, citing *In re Wands* 858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988).

The Examiner alleges that claims 2-14 are so broad as to encompass any or all other methods for screening COX-2 inhibitors. In the view of the Examiner, those skilled in the art will require an additional step in the method to confirm that COX-2 was indeed induced by the mutant G α 12, and it would require undue experimentation to determine and confirm that COX-2 was induced by the mutant G α 12. The Examiner also alleges that the specification provides no guidance with regard to the step. The Examiner also asserts that undue experimentation would be required because of lack of guidance and working examples, and unpredictability in predicting that COX-2 was induced by the mutant G α 12. The Examiner further alleges that the specification does not support the broad scope of the claims because the specification does not establish a step to link the induction of COX-2 by the mutant G α 12 by a confirming assay, and does not establish steps to confirm that proliferation or changes in prostaglandin or arachidonic acid production is due to the induction of COX-2 by the mutant G α 12.

The Examiner alleges at page 6 of the Office Action that "the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim." Multiple claims are being rejected, so Applicants are not sure which claim "this claim" refers to. Furthermore, neither the disclosure nor the claims specifically address polypeptides. Applicants assume that Examiner used the term "polypeptide" mistakenly and intended to use the term "test substance" and address the rejection accordingly.

Applicants respectfully disagree with the rejection for the following reasons.

First, the Examiner is reminded that MPEP § 2164.08 states "If a rejection is made based on the view that the enablement is not commensurate in scope with the claim, the examiner should identify the subject matter that is considered to be enabled." The Examiner did not identify the subject matter that is considered to be enabled in the Office Action.

A specification which discloses how to make and use a claimed invention is presumed to comply with the first paragraph of 35 U.S.C. § 112, unless there is a reason to doubt the objective truth of the specification. *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971). The initial burden of establishing a basis for denying patentability to a claimed invention therefore rests upon the examiner. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Thorpe*, 777 F.2d 695, 227 USPQ 964 (Fed. Cir. 1985); *In re Piasecki*, 745 F.2d 1468, 223 USPQ 785 (Fed. Cir. 1984). Here, the present specification clearly discloses a method for screening for a test substance as a COX-2 inhibitory agent, wherein COX-2 is induced by a mutant GTPase-deficient G α 12, and the Examiner has failed to rebut the assertions made therein.

Claims 2-14, as amended, do not encompass any and all methods of screening COX-2 inhibitors. Claims 2-14 encompass methods of screening for COX-2 inhibitors in indicator cells where the COX-2 is induced by a mutant G α 12. As described above, the claims have been amended to recite that the mutant α -subunit induces production of COX-2. Thus, the claims now recite a link between COX-2 production and the G α 12 mutant. The specification provides ample instructions and examples for preparing cells which express COX-2 by transfecting cells which do not express COX-2 with a mutant G α 12. Example 1 clearly demonstrates that in NIH3T3 cells, which do not normally express COX-2, transfection of the G α 12 mutant induces COX-2 expression at the mRNA and protein levels (FIGS. 2A, 2B, and 3). COX-2 was not induced in the controls not transfected with the G α 12 mutant. Thus, the specification provides ample guidance for determining that COX-2 is induced by the G α 12 mutant and provides numerous assays for determining that COX-2 is induced. Such assays are routinely used in measuring COX-2 activity in cells. For example, see DuBois et al. and Sheng et al., cited against the claims and discussed below. As described above, assays are exemplified which compare the effect of a COX-2 inhibitor on indicator cells expressing COX-2 with cells not expressing COX-2. The

MPEP clearly provides that as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement is fulfilled. See MPEP § 2164.01(b), citing *In re Fisher*, 427 F.2d 833, 839 166 USPQ 18, 24 (CCPA 1970).

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. MPEP §2164.01 (citing *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976)). Undue experimentation would not be required of a skilled artisan to make and/or use the full scope of the invention as recited in amended claims 2-14, because as described above, assays measuring COX-2 activity are routinely performed in the art.

Given the advanced state of the relevant art, ample disclosure, and the extensive reduction to practice provided in the specification as filed, amended claims 2-14 are enabled. Thus, Applicants respectfully request that the rejection of claims 2-14 under 35 U.S.C. § 112, first paragraph, be withdrawn.

D. Response to 35 U.S.C. § 102(b) anticipation rejection

Claim 1 stands rejected as allegedly anticipated by Sheng et al. (J. Clin. Invest., 1997, 99:9:2254-2259). Claim 1 has been canceled, therefore, the rejection as to this claim is now moot.

E. Response to 35 U.S.C. § 102(b) anticipation rejection or alternatively 103(a) obviousness rejection

Claims 2, 3, and 6-8 stand rejected as allegedly anticipated under 35 U.S.C. 102(b) by, or in the alternative, under 35 U.S.C. 103(a) as obvious over Sheng et al. The Examiner asserts that claims 2, 3, and 6-8 are drawn to a method of screening a test substance for COX-2 inhibitory activity by contacting a test substance with indicator cells and determining proliferation and prostaglandin levels, wherein the indicator cells express a GTPase-deficient mutant form of Gα12 comprising the mutation Q229L, which mutant has the capacity to induce production of arachidonic acid and COX-2 activity in indicator cells, and wherein a decrease in proliferation and prostaglandin levels indicates that the test substance has COX-2 inhibitory activity. The

Examiner alleges that Sheng discloses such an assay by contacting an indicator cell expressing COX-2 with a test substance and showing that the substance decreased cell proliferation and prostaglandin levels, when compared to control cells not treated with the test substance. The Examiner then concludes at page 8 of the Office Action that Sheng anticipates claims 2-14. Applicant respectfully points out that only claims 2, 3, and 6-8 stand rejected under 35 U.S.C. 102(b).

The Examiner admits at page 8 of the Office Action, that Sheng does not teach indicator cells expressing a GTPase-deficient mutant form of G α 12 with the capacity to induce arachidonic acid production and COX-2. However, the Examiner alleges that, because colon cancer cells have been shown to express high levels of COX-2, the high levels of COX-2 in Sheng's cells were inherently due to the expression of a GTPase-deficient mutant form of G α 12, namely G α 12QL, which mutant has the capacity to induce the production of arachidonic acid and COX-2. The Examiner then alleges that the indicator cells disclosed in the present application and the cells disclosed by Sheng are one and the same. The Examiner states that:

“[s]ince the Office does not have the facilities for examining and comparing applicants' indicator cells with the cells of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the cells of the prior does not possess the same material structural and functional characteristics of the claimed indicator cells),”

citing *In re Best*, 562, F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594.

For a reference to anticipate a claim, every limitation of that claim must identically appear, either expressly or inherently, in the reference. *In re Bond*, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). Absence of any claim element from the reference “negates anticipation.” *Kloster Speedsteel AB v. Crucible, Inc.*, 230 USPQ 81, 84 (Fed. Cir. 1986); *Rowe v. Dror*, 42 USPQ2d 1550, 1552 (Fed. Cir. 1992). Sheng does not disclose or teach every element of amended claims 2, 3, 6, 7 and 8.

Sheng does not disclose or teach methods of screening for substances which inhibit G α 12 mutant-induced COX-2 activity as measured by cell proliferation assays. Sheng discloses

methods of measuring tumorigenicity and tumor growth of colon cancer cells. The goal of Sheng was to show that COX-2 is involved in colorectal tumorigenesis and that tumor growth was inhibited by a COX-2 inhibitor (Sheng et al., page 2255, column 1, first paragraph). Sheng tested the effects of a COX-2 inhibitor on cancer cells by measuring colony formation in Matrigel (analogous to soft agar) and by measuring tumor formation in nude mice (see FIGS. 4 & 5). The colony formation assay is a classic assay used to determine the tumorigenicity of non-hemopoietic cells *in vitro*, based on the degree to which the cells have lost their control for anchorage-dependent growth. The assay is not intended to measure cell proliferation. Instead, it distinguishes cancer cells from non-cancerous cells, because non-cancerous cells have lost their anchorage-dependence. The nude mouse model used by Sheng measures tumorigenicity of cells *in vivo*, not cell proliferation. For example, Darnell et al., in a discussion referring to the characteristics of cancer cells, states that:

“if normal cells are suspended in a semisolid medium such as agar, they will metabolize but they will not grow. Most transformed cell lines have lost the requirement for adherence; they grow without attachment to a substratum, as indicated by their ability to form colonies when suspended as single cells in agar. This characteristic correlates extremely well with the ability of transformed cells to form tumors: cells that have lost anchorage dependence generally form tumors with high efficiency when they are injected into animals that cannot immunologically reject the cells.”

(p. 964, *Molecular Cell Biology*, 2nd ed., 1990, Darnell, Lodish, and Baltimore, Scientific American Books, Inc., New York; submitted herewith). Thus, the assays taught by Sheng are tumorigenicity assays, not proliferation assays. A normal cell, e.g., non-tumorigenic, even if expressing COX-2, will not proliferate in either of the assays used by Sheng. Thus, Sheng teaches away from claim 1.

Furthermore, Sheng does not disclose or teach measuring prostaglandin as an indicator of COX-2 activity in indicator cells where COX-2 expression is induced by a mutant Gα12, as claimed in claim 6. In fact, Sheng never mentions a relationship between arachidonic acid, prostaglandins, and COX-2 activity.

Contrary to the assertion of the Examiner, there is no evidence that the high levels of COX-2 in Sheng's cells were inherently due to expression of a GTPase deficient mutant form of Gα12. There is no evidence suggesting that Sheng's cells even have a mutant Gα12 gene.

The Examiner must provide a rationale or evidence tending to show inherency. MPEP § 2112. The Examiner has failed to do so in this case. The fact that a certain result or characteristic *may* occur or be present in the prior art is not sufficient to establish inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). Furthermore, “[t]o establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.” *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). An examiner must provide objective evidence or cogent technical reasoning to support the conclusion of inherency. *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). The Examiner has failed to meet this burden.

The assertion by the Examiner that the colon cancer cells of Sheng express high levels of Gα12 which induces the high levels of COX-2, is mere speculation. There is no reason to believe that all cancers expressing high levels of COX-2 do so because their Gα12 gene has been mutated and that the mutant Gα12 gene is now constitutively expressed. Inherency may not be established by mere probabilities or possibilities of something occurring. *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). As stated at page 9, lines 14-16, of the specification: “[p]rior to the present invention, it was not known that the Q229L mutation induces COX-2 transcription in cells.” There is no scientific basis or evidence to assume that the cancer cells of Sheng have a mutant Gα12 gene which is responsible for inducing the high levels of COX-2 expression seen in colon cancer cells. It is equally as plausible that the high levels of COX-2 in Sheng's cells is attributable to other factors, not the presence of a mutant Gα2. For example, most cancers are known to express autocrine growth factors, many of which are inducers of COX-2 expression. Some of the growth factors known to induce COX-2 include: Interleukin-1 (IL-1) and Transforming Growth Factor-α (TGF-α) (DuBois, page 1067, column

2); and IL-6, Tumor Necrosis Factor- α , TGF- β , Epidermal Growth Factor (EGF), Platelet-Derived Growth Factor (PDGF), and Fibroblast Growth Factor (FGF) (DuBois, page 1068, columns 1 and 2).

Sheng in fact teaches that increased levels of COX-2 expression in colon cancer cells may result from disruption of the well defined adenomatous polyposis coli (APC) tumorigenesis pathway in humans. Recent experimental evidence supports the hypothesis of Sheng. Hsi et al. showed that induction of COX-2 in colon cancer cells appears to be due to mutations in the APC gene (Hsi et al., 1999, Carcinogenesis 20:2045-2049, a copy of which is provided herewith; see also Sheng et al., page 2254, column 2, last sentence). Disruption of the APC tumorigenesis pathway is not the same as, or even remotely related to, mutation of the G α 12 gene.

Because Sheng does not disclose a method for screening a test substance for COX-2 inhibitory activity in cells expressing a mutant α -subunit of G12 which induces production of COX-2, every element of claims 2, 3, and 6-8 does not appear in Sheng, either expressly or inherently. Therefore, Sheng does not anticipate claims 2, 3, and 6-8 and the anticipation rejection as to these claims should be withdrawn.

Sheng does not render claims 2, 3, and 6-8, *prima facie* obvious under 35 U.S.C. § 103(a), for the following reasons.

Preliminarily, the three-prong test which must be met for a reference or a combination of references to establish a *prima facie* case of obviousness has not been satisfied in the instant matter. The MPEP states, in relevant part:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. MPEP § 2142.

To support a case of *prima facie* obviousness, a combination of references must: (1) suggest to those of ordinary skill in the art that they should make the claimed invention, and (2) reveal to those of ordinary skill in the art that they would have a reasonable expectation of success. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the

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reasonable expectation of success must be found in the prior art and not in Applicant's disclosure. *In re Dow Chemical Company*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). None of these criteria have been met here.

It would not be obvious to modify Sheng to arrive at the present invention. As admitted by the Examiner at page 8 of the Office action, Sheng does not teach or suggest a mutant G α 12 with the capacity to induce COX-2. That is not surprising, because the present application is the first to disclose that a mutant G α 12 induces COX-2 (page 9, lines 14-17). Sheng teaches cancer cells expressing high levels of COX-2 and methods to treat cancer cells. The claimed invention utilizes indicator cells expressing COX-2 induced by the mutant G α 12. In the absence of any prior teaching that the mutant G α 12 has the capacity to induce COX-2 expression, it could not have been obvious to introduce that mutation into a cell for that purpose. There could have been no motivation to modify Sheng to arrive at the present invention.

For the reasons discussed above, Sheng does not anticipate, or in the alternative render obvious, claims 2, 3, and 6-8. Therefore, Applicants request that the 102(b), or alternatively 103(a), rejection be withdrawn as to claims 2, 3, and 6-8.

F. Response to 35 U.S.C. § 103(a) obviousness rejection

Claims 4, 5, and 9-14 stand rejected as being unpatentable over Sheng et al. as applied to claims 2, 3, and 6-8 above, and further in view of DuBois et al. (FASEB J., 1998, 12:1063-1073) and the common knowledge in the cell biology and immunobiology techniques in the art. The Examiner asserts that claims 4, 5, and 9-14 are drawn to a method of measuring cell proliferation by tritiated thymidine uptake, a method of measuring prostaglandin levels by immunoassay, and to a method of screening a test substance for COX-2 inhibitory activity.

The Examiner admits at page 9 of the Office Action that Sheng does not disclose a tritiated thymidine uptake assay for the determination of cell proliferation as recited in claim 5, or a prostaglandin-immunoassay for measuring prostaglandin levels as recited in claims 9 and 10. The Examiner also admits that while Sheng discloses that COX-2 converts arachidonic acid to prostaglandins, it does not disclose that increased arachidonic acid is indicative of COX-2 inhibition, nor does it disclose arachidonic acid assays, as recited in claims 11-14. The Examiner

alleges that the DuBois review article teaches the involvement of COX-2 in a variety of human disorders, that arachidonic acid is converted to various prostaglandins by COXs, and that non-steroidal anti-inflammatory drugs (NSAIDS) which inhibit COXs lead to arachidonic acid accumulation.

The Examiner alleges that it would have been obvious to use a tritium labeled thymidine uptake assay to determine the decrease in cell proliferation and that one of skill in the art would be motivated to do so because it is a fool-proof technique. The Examiner further alleges that it would have been obvious to confirm the increase in the prostaglandin levels using the immunoassay because it is a standardized assay in the art and one of skill in the art would have been motivated to use it because of the high reliability of the assay. It is also alleged that it would have been obvious to measure the accumulation of arachidonic acid due to the simplicity of the assay.

It would not have been obvious to combine Sheng and DuBois. Examiner has provided no reasoning as to any motivation to combine Sheng and DuBois. The Examiner's assertion that there would be "motivation" to use the three types of assays recited in the claims because they are either fool-proof or easy, is not relevant to the application of an obviousness test. The "motivation" must be to combine the references. MPEP § 2142. The Examiner may not use hindsight based on the teachings of the specification.

As discussed above, Sheng teaches treating tumors with a COX-2 inhibitor, and does not teach a method of screening for substances which have COX-2 inhibitory. Sheng does not teach cell proliferation assays or arachidonic acid assays. Moreover, as admitted by the Examiner, Sheng does not teach or suggest using a mutant G α 12 protein to induce COX-2 expression in cells not expressing COX-2, and then screening for COX-2 inhibitors with such indicator cells. In fact, Sheng never mentions the mutant G α 12.

DuBois, as a review article, merely teaches general information about COX-2 and does not remedy the deficiencies of Sheng. DuBois does not teach or suggest using cells containing a mutation in the G α 12 protein as indicator cells in an assay to screen for potential COX-2 inhibitors. The combination of Sheng and DuBois does not result in the claimed invention

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Therefore, the claimed invention would not have been obvious from the combination of Sheng and DuBois.

Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of claims 4, 5, and 9-14 be withdrawn.

G. Conclusion

Based on the foregoing, all claims are believed in condition for allowance. An early and favorable action toward that end is earnestly solicited.

Respectfully submitted,

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